

vectors that arise through recombination. Also provided by the invention are methods of using the vectors to treat pathologies, including cancer, in mammals.

### **Status of the Application**

Claims 16-24 and 26-41 are pending with entry of this amendment, with claims 16-24 and 26-31 previously in the application and entry of new claims 32-41 respectfully requested.

Claims 16-21 and 26-41 stand rejected under 35 USC § 112, first paragraph. Claim 23 stands rejected under 35 USC § 112, second paragraph.

### **The Amendments**

Applicants respectfully request entry of the above amendments to the application. The amendment to page 1 of the specification provides corrected and updated information regarding the parent applications. In the continuing information provided in the preliminary amendment filed October 28, 1997, an incorrect serial number and filing date were given for one of the priority applications. Specifically, Ser. No. 08/246,006, filed May 19, 1994 should have been listed instead of Ser. No. 08/233,777, filed May 19, 1994. The status of each parent application is also provided.

The amendment at page 19 line 7 corrects the description of the subject matter shown in Table 1. Specifically, Table 1 obviously shows an amino acid sequence, not a “coding sequence,” which would be a nucleotide sequence.

The amendment at page 20 line 3 corrects an obvious error in the amino acid sequence of p53. In particular, the amino acids that precede the initial methionine (“M”) of p53. Those of skill in the art would have known that the amino acids shown in Table 1 that precede that encoded by the initiation codon of the p53 gene are not actually part of the p53 polypeptide. This is particularly evident given that these mistakenly included amino acids are interrupted by stop codons.

All of the remaining amendments to the specification are necessary because Applicants are unable to locate the original photographs that are shown in originally filed Figures 5A, 5B, 6A, 6B, 6C, 9, 13A, and 13B. Accordingly, Applicants request cancellation of these

figures. The amendments to the specification are all directed to removing references to the deleted figures and renumbering of the subsequent figures as required by M.P.E.P. § 608.02(t).

The drawings that have been canceled are not necessary for the understanding of the subject matter to be patented; therefore, they are not required under 35 U.S.C. §113. The canceled figures merely provide a visual result for experiments described in the specification. Furthermore, the results of the experiments are also given in the specification. For example, Figures 5A and 5B showed protein expression in tumor cells. This experiment and the results are described, for example, on page 37, lines 10-29 and at page 38, line 14. Figure 6A and 6B showed a p53 dependent morphology change, which is described in detail, for example, on page 37, line 30 through page 38, line 17. Figure 9 showed expression of RNA in established tumors. This is described, for example, on page 40, line 22 through page 41, line 14. Lastly, Figures 13A and 13B showed CAT expression and are described, for example, on page 50, line 11 through page 51, line 3. The canceled figures also do not touch on the claims or their scope.

The above amendments add no new matter to the application. The amendments merely remove some unnecessary drawings and references thereto, or correct readily apparent errors in the application. The insertion on page 41, line 2 was originally present in the legend for Figure 9 (page 8 lines 15-22).

The newly added claims likewise add no new matter to the application. The new claims find support throughout the specification, and in particular as follows:

- Claims 32, 36, and 37: originally claim 16; p. 14 line 30 to p. 15 line 3
- Claims 33, 34, 38, 39: p. 24, lines 27-35
- Claims 35 and 40: p. 22, lines 16-21 and p. 36 lines 8-11
- Claim 41: p. 27 line 34 to p. 28 line 2.

#### **The 35 U.S.C. § 112, First Paragraph Rejection**

Claims 16-24 and 26-31 stand rejected under 35 USC § 112, first paragraph, because the specification allegedly does not describe the claimed subject matter in such a way so as to enable one of ordinary skill in the art to make and use the invention. Applicants respectfully traverse.

**A. The rejection is based on an asserted lack of patentable utility, but does not establish a *prima facie* case**

The basis for this rejection is not that Applicants have failed to teach how to carry out the steps necessary to administer adenoviral vectors to humans or other animals, or how to make such vectors. Indeed, such assertions would have been inappropriate, because Applicants' specification provides much detail as to suitable vectors, methods and locations of administration, appropriate dosages, and the like. For example, the specification provides a detailed description of suitable adenoviral vectors on pages 13-16, including suitable promoters, *etc.* for use in expressing a gene of interest. Significantly, the vectors encompassed by Applicants' claims provide an improvement over previously available adenoviral vectors. In particular, the vectors have a partial or total deletion of a protein IX-encoding DNA sequence, which reduces the risk of wild-type (*i.e.*, replication competent) adenoviral vectors in virus preparations for use in diagnostic and therapeutic applications. Tumor suppressor and suicide genes that are suitable for inclusion in the adenoviral vectors used in Applicants' claimed methods are also described in the specification. For example, tumor suppressors are described at page 16, line 21 to p. 20, line 19. Suicide genes are described at, for example, page 27 line 11 to page 28 line 2. The methods necessary to assemble these components into a vector as taught by Applicants' specification do not require undue or excessive experimentation; each step in the process involves a method that is routinely carried out by those of skill in the art.

Nor is undue experimentation required to administer the adenoviral vectors according to Applicants' claimed methods. Applicants' specification teaches pharmaceutically acceptable carriers that are suitable for use in the claimed methods. *See, e.g.*, p. 20, line 35 to p. 22, line 27. Moreover, at the time of Applicants' filing date, those of skill in the art had accumulated much knowledge as to how to administer vectors intended for gene therapy of cancer. Applicants' specification at p. 25 cites Larrick and Burck (1991) *Gene Therapy: Application of Molecular Biology*, Elsevier Science Publishing Co., Inc., New York, and Kriegler (1990) *Gene Therapy and Expression: A Laboratory Manual*, W.H. Freeman and Company, New York, as examples of references that teach methods for gene therapy. Applicants' specification provides additional teachings as to how to administer adenoviral vectors to accomplish the claimed methods. For example, at page 26, lines 10-16, Applicants'

specification teaches that the viral vectors can be administered intravenously, by intratumoral injection, by intraperitoneal administration, among other methods. Applicants' specification also teaches suitable dosages and treatment regimes (*e.g.*, at page 26 lines 25-35). Again, each of these administration methods are routinely carried out by clinicians; no undue experimentation is required.

Thus, no step that is required to practice the claimed methods, *e.g.*, making an adenoviral vector and administering the vector to a mammal, requires undue experimentation. Therefore, it is clear that this rejection, although couched in terms of undue experimentation allegedly being required to practice the invention, is actually based on a belief that gene therapy in general lacks utility. However, the Office Action does not meet the requirements for establishing a lack of utility rejection.

As acknowledged by the MPEP, in the rare cases in which courts have sustained utility rejections under 35 USC § 101, the rejection was maintained "either because the applicant failed to disclose any utility for the invention or asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art" (MPEP § 2107, emphasis in original).

The Federal Circuit has explicitly held that "the purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking or involve implausible scientific principles." *In re Brana*, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). The MPEP states that "[t]hese general principles are equally applicable to situations where an applicant has claimed a process for treating a human or animal disorder. In such cases, the asserted utility is usually clear, the invention is asserted to be useful in treating the particular disorder. If the asserted utility is credible, there is no basis to challenge such a claim on the basis that it lacks utility under 35 USC 101." (MPEP § 2107 at p. 2100-34, emphasis original). The use of gene therapy for the purpose of treating cancer likewise is not inherently unbelievable and does not involve implausible scientific principles. Therefore, a 35 USC § 101 rejection of Applicants' claims would be improper.

Given that a 35 USC § 101 rejection is improper, a “lack of utility” rejection under 35 USC § 112, first paragraph is also improper. According to MPEP § 2164.07, “[a] 35 U.S.C. 112, first paragraph, rejection should not be imposed or maintained unless an appropriate basis exists for imposing a rejection under 35 U.S.C. 101. In other words, Office personnel should not impose a 35 U.S.C. 112, first paragraph, rejection grounded on a “lack of utility” basis unless a 35 U.S.C. 101 rejection is proper” (emphasis added). Therefore, because the rejection is based upon an asserted lack of utility but does not satisfy the requisite standard for making such rejection, Applicants respectfully submit that the rejection is improper and should be withdrawn for this reason alone.

***B. The PTO has not established prima facie lack of enablement***

The PTO has the initial burden of making a *prima facie* case of showing that a claimed invention lacks utility under 35 USC § 101/112, first paragraph (MPEP § 2107) or is not enabled under 35 USC § 112, first paragraph (MPEP § 2164.04). The rejection attempts to meet this burden by applying the Wands/Forman factors. However, Applicants respectfully submit that the instant rejection does not meet the PTO’s burden of establishing a *prima facie* case of non-enablement for the following reasons, which are organized under the headings used in the Office Action.

**1. Unpredictability of the art**

The rejection asserts that the gene therapy art was extremely unpredictable at the time Applicants’ invention was made. In support of this rejection, three references are cited. However, Applicants respectfully submit that these references, taken alone, do not provide a true understanding of the state of the art of gene therapy, and in particular of the use of gene therapy to treat cancer. A much more accurate picture of the state of the art of gene therapy is provided by the number of gene therapy clinical trials that are currently underway, including Phase II and Phase III trials. As of December 1, 1998, 366 gene therapy trials have been published or are underway, of which 230 are directed to cancer gene therapy (Wiley Clinical Trials Database, <http://www.wiley.com/genetherapy/diseases.html>). Of the 367 gene therapy clinical trials, 32 are

in Phase II, and 2 are in Phase III. Fifty-nine of the trials used adenoviral vectors. Importantly, at least 20 of these gene therapy clinical trials had commenced prior to Applicants' priority date. *Id.*

Just obtaining FDA approval to conduct clinical trials in humans requires a demonstration of pharmaceutical efficacy that is more than sufficient to satisfy the requirements for patentability under 35 USC § 112 and 101. As stated in the MPEP, “[b]efore a drug can enter human clinical trials, the sponsor, often the applicant, must provide a convincing rationale to those especially skilled in the art (e.g., the Food and Drug Administration) that the investigation may be successful. . . . Thus, as a general rule, if an applicant has initiated clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility” (MPEP § 2107.02, emphasis in original). In the face of the avalanche of clinical trials that have been approved by the FDA, no basis exists for the Office Action’s position that the state of the art for gene therapy in general is insufficiently unpredictable for patentability.

## 2. State of the Art

The rejection then asserts that the gene therapy art at the time of Applicants’ invention was poorly developed. Two of the same references cited in support of the previous point are cited in support of this factor. The rejection states that these two references establish that “no gene therapy protocol had been unambiguously proven to be successful *in vivo*” (Office Action, p. 3). However, this is irrelevant, as patentable utility does not require that an invention be “unambiguously proven” *in vivo*. All that is required is that some pharmaceutical activity be established, either by *in vitro* or *in vivo* tests. MPEP § 2107.02. Applicants’ comments regarding point 1 above are equally applicable to this ground of the rejection.

## 3. Number of Working Examples

According to the rejection, Applicants present no working examples. This statement ignores the experimental data that is provided in the specification. For example, the specification provides experimental data which demonstrate that an adenovirus vector that expresses p53 was effective in greatly reducing the growth of established tumors and

significantly enhancing survival times of animals having tumors (*see, e.g.*, Applicants' specification at pp. 41-42, also Figures 10A and 10B). Another example provided *in vitro* and *in vivo* results demonstrating pharmaceutical activity of methods that employed an adenovirus vector that expressed a suicide gene (Experiment III, pp. 45-54, results at pp. 52-54). These results are discussed in more detail below.

According to the MPEP, "an *in vitro* or *in vivo* animal model in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention." MPEP § 2164.02. It is the Examiner's burden to "give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model." *Id.* In the instant case, no reasons are set forth.

#### 4. Amount of Guidance Presented by Applicants

The Office Action bases its analysis of this factor on whether or not the *in vitro* and *in vivo* data provided by Applicants relate to treatment of cancer in humans. The legal standard for judging whether data from an *in vitro* assay is sufficient to satisfy the enablement requirement of 35 USC § 112, first paragraph is whether one of skill in the art would accept the *in vitro* data as reasonably correlating to the asserted *in vivo* activity. A rigorous or an invariable exact correlation is not required. MPEP § 2107.02, *citing Cross v. Iizuka*, 224 USPQ 739, 747 (Fed. Cir. 1985). Again, it is the Examiner's burden to "give reasons for a conclusion of lack of correlation for an *in vitro* or *in vivo* animal model." MPEP § 2164.02. Absolutely no reasons are provided, so the Examiner has not satisfied this burden.

Although not required to further supplement their presumptively correct disclosure, Applicants provide the following additional information and argument. The model system used in the experiments described in Applicants' specification are of a type that is accepted by those of skill in the art as being reasonably correlated with therapeutic or pharmacological utility of a cancer treatment. Applicants' Experiment II, for example, utilized nude mice into which H69 (small cell lung carcinoma cells) had been introduced, resulting in the establishment of tumors. In *In re Brana*, the Federal Circuit expressly recognized that tumors that arise from introducing tumor cells into nude mice provide an acceptable model system for establishing therapeutic or pharmacological utility of a potential cancer treatment. Moreover, the

H69 cells used in Applicants' experiments are derived from an actual tumor (a small cell human lung carcinoma from a 55 year old male) and are accepted for use in screening of cancer treatments by the National Cancer Institute (*see*, attached document from SRI International which describes cancer screening services and includes the cell line "NCI-H69" for lung cancer screening; Exhibit 1). In *Brana*, the Federal Circuit gave significant weight to the use of a cell line that was recognized as suitable by the NCI (*In re Brana*, 34 USPQ2d at 1442).

Furthermore, Applicants' claimed methods were found to exhibit encouraging results in an ongoing Phase I clinical trial (*see*, attached press release of Schering-Plough, November 23, 1998; Exhibit 2). The MPEP states that "as a general rule, if an applicant has initiated clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility" (MPEP § 2107.02, emphasis in original). Therefore, the subject matter of Applicants' claimed methods must be presumed to satisfy the standard for utility under 35 USC § 112, first paragraph.

#### 5. Scope of the Claims

According to the rejection, the claims read broadly on treatment of any of thousands of different pathologies in animals or humans. However, Applicants note that the pending claims are limited to tumors and tumor cells. Furthermore, some of Applicants' claims are directed to narrower embodiments than the broadest claims. For example, claim 24 is limited to a particular mode of administration (intratumoral), claim 29 is limited to a particular type of tumor cells (hepatocellular carcinoma). No discussion is provided by the Office Action as to the narrower embodiments.

#### 6. Nature of the Invention

This factor is merely a repetition of the first and second factors discussed above and does not add new evidence or reasoning to support the rejection. Therefore, Applicants' responses to the first and second factors are applicable to this ground of the rejection.

7. Level of Skill in the Art

Applicants agree that the level of skill in the gene therapy art is high. Applicants do not agree, however, that those of preeminent skill in the art were unable to reduce to practice successful gene therapy years after the priority date. To the contrary, as discussed above, many gene therapy studies (including those of Applicants) have shown sufficient pharmaceutical utility to satisfy the enablement/utility requirement of 35 USC § 112, first paragraph.

In summary, Office Action does not establish a *prima facie* case of nonenablement.

**C. *Applicants' Experimental Results are Sufficient to Overcome a Prima Facie Case of Non-Enablement***

Even if the Office Action had established a *prima facie* case of non-enablement, which it has not, Applicants' specification contains sufficient *in vitro* and *in vivo* experimental data to overcome the *prima facie* case. According to the MPEP, “[i]f reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition, or process.” MPEP § 2107.02(a)(emphasis added).

Applicants' specification demonstrates that the claimed methods can reduce tumor growth *in vivo*. Experiment II (pp. 32-45) describes an experiment in which an adenoviral vector of the invention which carried a gene encoding the tumor suppressor p53 was found to greatly reduce the growth of established tumors and significantly enhance survival times of animals having these tumors (see, e.g., Applicants' specification at pp. 41-42, also Figures 10A and 10B). The last of the control adenovirus-treated animals died on day 83, while all five animals treated with a p53-expressing vector were still alive 130 days after tumor cell inoculation.

Applicants' specification also provides experimental results from an experiment in which a different *in vivo* system was used to demonstrate the efficacy of an adenovirus that expressed a suicide gene (Experiment III, pp. 45-54, results at pp. 52-54). Adenoviral vectors that express HSV-tk were introduced into three different hepatocarcinoma lines *in vitro* and, in conjunction with ganciclovir treatment, shown to inhibit cellular proliferation (Figure 14, Table 2 at p. 53). An *in vivo* experiment in which established tumors in mice were treated with the

adenoviral vectors and ganciclovir in accordance with the methods of the invention resulted in a reduction of tumor size at day 58, although the difference in tumor size did not reach statistical significance. Thus, Applicants have established that the claimed methods exhibit pharmacological utility in both *in vitro* and *in vivo* systems.

In summary, *prima facie* non-enablement has not been established by the instant Office Action. Moreover, Applicants' have provided *in vitro* and *in vivo* data which demonstrate that the claimed methods have pharmacological utility. Under well-established case law, these data would be sufficient to overcome a *prima facie* case of non-enablement, had such case been established. Therefore, Applicants respectfully submit that this ground of rejection is improper and should be withdrawn.

**D. Applicants' New Claims Satisfy the Enablement Requirement of 35 USC § 112, First Paragraph**

Applicants have added to the application new claims 32-41, which are directed to methods for obtaining expression of a tumor suppressor gene in a cell (claims 32-36) and for obtaining expression of a suicide gene in a cell (claims 37-41). As do the previously pending claims, Applicants' new claims satisfy the enablement requirement of 35 USC § 112, first paragraph. The methods of claims 32-41 are fully supported by experimental data that is present in Applicants' specification. For example, experimental data at page 37 demonstrate that p53 protein is expressed by cells into which adenoviral vectors that contained the p53 gene were introduced.

Moreover, although the newly added claims encompass gene therapy, the claimed methods also find use for applications other than cancer therapy. For example, the methods are useful for "safe recombinant production of diagnostic and therapeutic polypeptides and proteins . . ." (Applicants' specification, p. 14, lines 30-32). Such uses of the claimed methods are sufficient to satisfy the utility requirement of 35 USC §§ 101/112, first paragraph, even aside from the therapeutic uses of the methods. As stated in the MPEP, "[r]egardless of the category of invention that is claimed (e.g., product or process), an applicant need make only one credible assertion of specific utility for the claimed invention to satisfy 35 U.S.C. 101 and 35 U.S.C. 112;

additional statements of utility, even if not "credible," do not render the claimed invention lacking in utility." MPEP § 2107.01.

**The 35 U.S.C. § 112, Second Paragraph Rejection**

Claim 23 stands rejected under 35 USC § 112, second paragraph as being indefinite. Applicants have amended claim 23 as kindly suggested by the Examiner to replace "and" with --or--. This is believed to obviate this ground of rejection.

**CONCLUSION**

In view of the foregoing, Applicants believe that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

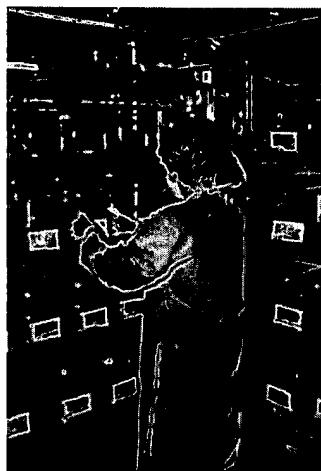
If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned attorney at (415) 576-0200.

Respectfully submitted,



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- **Prostate** (LN Cap, DU145)
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- **Skin** (A431, CaSki, SiHa, HN-5, UM-SCC22B, SCC13, SCC9, SCC25, SCC25CP)
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## SCHERING-PLOUGH PRESS RELEASE

### SCHERING-PLOUGH REPORTS FINDINGS OF p53 GENE THERAPY STUDIES AT CONFERENCE ON GENE THERAPY OF CANCER ANNUAL MEETING

**SAN DIEGO, November 23, 1998** — Schering-Plough Research Institute today reported that interim results from ongoing Phase I clinical studies of its recombinant adenovirus encoding human p53 (rAd/p53) gene therapy confirm p53 transgene expression in patients with various types of cancer following intrahepatic and intraperitoneal administration. Expression of the normal p53 tumor-suppressor gene in human cancers lacking functional p53 genes is an important step in the clinical development of rAd/p53 as a cancer-fighting agent.

Interim results from the Phase I studies were presented here by study investigators at the Seventh International Conference on Gene Therapy of Cancer. Schering-Plough is the first to report results of intrahepatic and intraperitoneal adenoviral p53 gene therapy. In total, investigators presented findings of seven preclinical and clinical studies involving Schering-Plough's gene therapy programs.

The Phase I studies were designed to measure toxicity, gene expression and immune response in patients with evidence of p53 mutation in their cancer. Patients with primary or metastatic liver tumors received varying doses of rAd/p53 by injection into the hepatic artery. Patients with ovarian cancer received varying doses of rAd/p53 by injection into the peritoneal cavity. These patients were treated with single-dose and/or multi-dose regimens of rAd/p53 alone or in combination with chemotherapy.

Analysis of patients' tumors evaluated to date demonstrated in a majority of patients the successful delivery of wild-type (normal) p53 to tumors expressing abnormal p53, despite pre-existing antibodies to the adenovirus. These studies also demonstrated that the addition of chemotherapy to rAd/p53 gene therapy was tolerable. Nearly all patients experienced mild to moderate side effects such as fever, nausea and anemia.

"These results confirm p53 gene therapy's promise as a potential

treatment for a variety of cancers," said Jean-Jacques Garaud, M.D., senior vice president of worldwide clinical research and clinical operations, Schering-Plough Research Institute. "While the results of these studies are preliminary, we are greatly encouraged by these findings and are initiating Phase II/III studies for intraperitoneal administration of rAd/p53 in patients with ovarian cancer and Phase II studies for intrahepatic arterial administration in patients with primary or metastatic liver tumors."

Schering-Plough's p53 gene therapy uses a genetically engineered adenovirus — a virus in the same family as the virus that causes the common cold — to provide normal p53 function to tumor cells deficient in p53 tumor suppressor activity. Preclinical studies have demonstrated that the introduction of a normal p53 gene into a malignant cell, where the p53 gene is absent or mutated, can suppress the cell's malignant state or result in apoptosis (programmed cell death). This therapeutic approach may have a potential application in at least 50 percent of all human tumors.

Schering-Plough's p53 gene therapy program began in 1994 through a research collaboration with Canji, Inc., a leading developer of gene-related therapeutic products. Canji was acquired by Schering-Plough in 1996 and is now Schering-Plough Research Institute's center for gene therapy discovery.

Schering-Plough Research Institute is the pharmaceutical research and development arm of Schering-Plough Corporation (NYSE: SGP), a research-based company engaged in the discovery, development, manufacturing and marketing of pharmaceutical and health care products worldwide.

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